The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer

Maura L. Gillison et al

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 90-03

A PHASE III RANDOMIZED STUDY TO COMPARE TWICE DAILY HYPERFRACTIONATION, ACCELERATED HYPERFRACTIONATION WITH A SPLIT AND ACCELERATED FRACTIONATION WITH CONCOMITANT BOOST TO STANDARD FRACTIONATION RADIOTHERAPY FOR SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

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INDEX

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SCHEMA

STRATIFY

Site-oral cavity
oropharynx
hypopharynx
larynx

Stage- N0 vs. N+

KPS- 90-100
60-80

RANDOMIZE

Arm 1: Standard Fractionation:
2 Gy/Fx, Q.D. 5 Days/wk
Total Dose: 70 Gy/35 Fx/7 wks

Arm 2: Hyperfractionation:
1.2 Gy/Fx, b.i.d. (> 6 hours apart, 5 days/wk
Total Dose: 81.6 Gy/68 Fx/7 weeks

Arm 3: Accelerated Hyperfractionation with split:
1.6 Gy/Fx b.i.d. (> 6 hours apart), 5 days/wk
Total Dose: 67.2 Gy/42 Fx/6 wks with a 2 week rest after 38.4 Gy

Arm 4: Accelerated fractionation with concomitant boost:
a. Large Field:
32.4 Gy/18 fx/3 1/2 wks
1.8 Gy/fx/day, 5 days/week
b. Concomitant Boost:
- 1.5 Gy/fx/day to boost field for 18.0 Gy/12 fx > 6 hours after large field treatment
- Large Field Treatment to receive 21.6 Gy/12 fx, 1.8 Gy/fx
c. Total Dose:
72.0 Gy/42 fx/6 wks

Eligible:

Sites:	Oral Cavity, Oropharynx, Hypopharynx, Supraglottic Larynx
Age:	≥ 18
Histology:	Squamous cell or lymphoepithelioma
Stage:	AJC Stage III or IV (Stage II base of tongue and hypopharynx), no distant metastases
Karnofsky Status:	≥ 60
Prior Therapy:	No prior radiotherapy, chemotherapy or surgery other than biopsy.

Required Sample Size: 1080

4/15/95

2.0 OBJECTIVES

2.1 To determine whether hyperfractionation and/or accelerated fractionation improves the local-regional control rate of advanced squamous cell carcinomas of the head and neck.

2.2 To determine the disease-free survival and actuarial survival of patients treated with the different fractionation schemes.

2.3 To determine the acute and late toxicity of each fractionation schedule.

2.4 To test prospectively whether there exists any difference between the treatment regimens with respect to the Quality of Life endpoints. **(added 3/17/92)**

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically proven squamous cell carcinoma (includes lympho-epithelioma and anaplastic carcinoma) arising in eligible head/neck regions and stages (see Appendix III). Where N + disease is based on presence of nodal disease found only on CT or MRI scans, i.e. not palpable on clinical examination, the size of the node(s) detected with CT or MRI scans must be $\geq$ 1.0 cm in its minimal axial diameter, or contain necrotic regions regardless of size. Biopsy may be obtained from the primary or regional lymph nodes. **(revised 3/15/93)**

3.1.2 General condition: In the estimation of the investigator the patient must be medically able to withstand a course of definitive radiotherapy.

3.1.3 The minimum age for entry is 18 years.

3.1.4 Karnofsky performance status **≥ 60** (Appendix II).

3.1.5 Patients must not have received previous surgery except biopsy, for the tumor under study. Patients with a prior malignancy (other than non-melanoma skin cancer) are ineligible, unless previous cancer was treated 5 years or more prior to the current tumor and patient has remained continually disease free.

3.1.6 Patient must sign a study-specific informed consent form.

3.1.7 Laboratory values within 2 weeks of entry.

3.2 Ineligibility Criteria

3.2.1 Histology other than squamous cell carcinoma, or one of its histologic subtypes (includes lympho-epithelioma/anaplastic). Adenocarcinomas are excluded.

3.2.2 Evidence of metastases (below the clavicle or distant) by clinical or radiographic means.

3.2.3 Patients with prior or simultaneous primaries (see 3.1.5)

3.2.4 Karnofsky status **< 60**

3.2.5 Patients with prior chemotherapy or surgery (other than biopsy) are ineligible.

3.2.6 Prior radiotherapy of the head and neck.

3.2.7 Patients treated in planned combined pre- or post-operative programs are excluded; however, post RT neck dissections are allowed if lymph nodes are > 3 cm (prior to RT)or persist after treatment. (See Section 8.2). If tumor persists at the primary site 6 weeks following completion of irradiation, salvage surgery, if possible, may be performed.

3.2.8 Tumors arising in sites or stages other than those listed in Appendix III; glottic and subglottic sites are ineligible.

3.2.9 Patients for whom follow-up is unlikely to be carried out by the member radiation therapist.

3.2.10 Patients in whom combined external beam irradiation and interstitial implant boost are planned are excluded.

6.0 RADIATION THERAPY

6.1 Physical Factors

6.1.1 Equipment: linear accelerators with appropriate photon and electron energies for supplemental boosting to the nodes or $Cobalt^{60}$ machines must be used.

6.1.2 Selection of the appropriate photon energy should be based on optimizing the RT dose distribution within the target volume and minimizing dose to normal tissue. Photon energies > 6 MMV may be utilized in dual energy beam arrangements only if one beam is $\leq$ 6 MV. **(revised 8/17/92)**

6.1.3 Treatment distance must be $\geq$ 80 cm S.S.D (or S.A.D for isocentric techniques).

6.2 Localization Requirements

6.2.1 Simulation: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. **Radio-opaque markers should be used to delineate the extent of nodal disease and whenever possible, the primary tumor.** The use of customized blocks to shape the treatment fields is recommended. Simulation films of each field, initial port films, and the calculation form will be sent to

RTOG Headquarters in the first week of therapy, together with the treatment prescription for radiation therapy quality assurance review.

6.2.2 Verification: Beam verification (port) films must be obtained for each field. This should be repeated at least every two weeks during treatment and whenever any field adjustments are made. Port films of each field must be submitted to the RTOG Headquarters.

6.3 Target Volume Irradiation Portals

6.3.1 A combination of lateral opposing fields, anterior and lateral wedged fields, or several beam-directed fields, will be used for the primary tumor site at the discretion of the investigator for the case. A single anterior A-P field will be used to treat the neck below the fields for the primary tumor. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s). All fields must be treated on each treatment day. The lower neck and supraclavicular field should abut the primary field at the skin. For oral cavity and oropharynx primaries, a midline block 2 cm wide and at least 2 cm in length on the skin surface will be placed in the anterior lower neck field to shield the larynx and the spinal cord in the junction region. For larynx and hypopharynx primaries, a lower lateral block, 2 cm in height should be placed in the lateral upper neck fields to shield the areas of potential overlap of diverging beams over the spinal cord.

The primary treatment fields should encompass the primary tumors with adequate margins along with sites of known and/or suspected lymph node disease in the upper neck. There should be a minimum of 2-3 cm margin around the primary tumor and positive node(s) and should include upper neck nodes to be irradiated electively for the initial target volume. At least two field reductions are recommended for all four arms. The first field reduction off the spinal cord occurs at 40-44 Gy for arm 1, 45.6 Gy for arm 2 and 38.4 Gy for arm 3. The second field reduction occurs at 50-60 Gy for arm 1, 50.4-60 Gy for arm 2, and 51.2-60.8 Gy for arm 3. A third field reduction at 69.4 Gy is recommended for arm 2. There should be a minimum of 2 cm margin around the initial tumor volume and positive neck node(s) for the first field reduction and a minimum of 1-1.5 cm margin around the initial tumor volume and positive neck node(s) for the second field reduction and a minimum of 1 cm margin for the third field reduction. For arm 4, there should be a minimum of 1-1.5 cm margin around the initial tumor volume and positive neck node(s) for the concomitant boost field beginning at 32.4 Gy. The large field is reduced off the spinal cord at 45 Gy. **(revised 8/17/92)** The primary treatment fields by tumor site and the lower neck field are as follows:

6.3.2 Oral tongue and floor of mouth

6.3.2.1 **The lateral fields should include the primary tumor, the submandibular and upper jugular nodes. Irradiation of the posterior chain is not indicated unless there are clinically positive cervical nodes.**

6.3.3 Anterior tonsillar pillar and retromolar trigone.

6.3.3.1 **The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T_3 or T_4.**

6.3.3.2 **Both ipsilateral and contralateral posterior cervical nodes must be irradiated if there are clinically positive nodes in the anterior chain.**

6.3.4 Oropharynx

6.3.4.1 **The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T3 or T4.**

6.3.4.2 **Both the ipsilateral and contralateral posterior cervical nodes must be irradiated if there are clinically positive cervical nodes in the anterior chain.**

6.3.5 Supraglottic larynx

6.3.5.1 **The upper border of the field includes the nodes in the upper jugular region. One cm of the mandible is to be included to obtain adequate coverage.**

6.3.5.2 **If there is involvement of the pyriform sinus and/or lateral hypopharyngeal wall, the superior border is placed at the base of the skull (above C1)to include the retropharyngeal nodes.**

6.3.5.3 **The lower border of the field encompasses the larynx usually at or below the level of C5.**

6.3.5.4 **The ipsilateral posterior nodes should be treated for T3 and T4 lesions.**

6.3.5.5 **Both ipsilateral and contralateral posterior nodes should be treated if there are clinically positive nodes in the anterior chain.**

6.3.6 Hypopharynx

6.3.6.1 **The superior border is placed at the base of skull (above C1) to include the retropharyngeal nodes. Nodes in the upper jugular region and posterior triangle are included. One cm of the mandible is to be included to obtain adequate coverage.**

6.3.6.2 The lower border of the field encompasses the lower border of the cricoid cartilage.

6.3.7 Lower neck

6.3.7.1 **A single anterior lower neck field will be used to treat the neck and the supraclavicular fossa below the fields for the primary tumor. When there is (are) positive node (s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s). (See Section 6.3.1)**

6.3.7.2 **The lower border of the field will be just below the clavicle or 1 cm below the clavicle when there are positive nodes in the supraclavicular fossa.**

6.3.7.3 **For all patients with clinically positive nodes greater than 6 cm, positive supraclavicular nodes, or pyriform sinus tumors that are T_3 or T_4 or have clinically positive nodes, a mediastinal T field should be used.**(8/17/92) **The lateral limbs of the T extend to 1 cm below the clavicle and the central portion of the field extends 5 cm more inferiorly to include the upper mediastinum.**

6.4 Dose Calculation

6.4.1 Dose to the supraclavicular field is calculated at 3 cm depth and to the upper mediastinum at 5 cm depth. Complete isodose curves are required. Lithium fluoride dosimetry is recommended as a further check on tumor dose. Cumulative isodose distributions at the level of tumor center, and a copy of the treatment record indicating cumulative doses, and boost field simulation and portal films must be submitted at the completion of radiotherapy.The specification of the target dose is in terms of a dose to a point at or near the center of target volume. The following portal arrangement are specified for photon beams:

6.4.1.1 **For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.**

6.4.1.2 **For arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.**

6.4.1.3 **Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).**

6.4.2 Tissue equivalent compensators should be used to ensure homogeneity of dose distribution so that variation within the target volume does not exceed 10% of the target dose.

6.4.3 Boost doses will be specified at the actual site(s) of gross primary and nodal disease.

6.5 Dose Fractionation

6.5.1 Standard Fractionation (Arm 1) (revised 8/17/92, 3/15/93)

Treatment to the primary tumor and upper neck will be given at 2.0 Gy per fraction, once a day, five days a week to a total dose of 70 Gy in 35 fractions in seven weeks. Fields must be reduced to exclude the spinal cord at 40 -44 Gy at the midplane. However the entire neck must be irradiated to a dose of 44 Gy (even in N0 stage) at anatomical levels of lymph node spread usually 2-4 cm below the skin surface. Clinically positive neck nodes should receive a minimum dose of 70 Gy in 35 fractions in 7 weeks. To supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include additional electron beam ($\geq$ 9 MeV) to the posterior neck, wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 44 Gy at 3 cm depth.

The anterior lower neck field will be treated at 2 Gy per fraction at 3 cm depth, once a day, to a total dose of 44 Gy in 22 fractions in 4.5 weeks. The total dose to the primary tumor and clinically positive nodes will be 70 Gy in 35 fractions in 7 weeks.

6.5.2 Hyperfractionation (Arm 2) (revised 3/15/93)

Treatment to the primary and upper neck will be given at 1.2 Gy per fraction, twice a day with a minimum of a 6 hour interval, 5 days a week, to a total dose of 81.6 Gy in 68 fractions in 7 weeks. Fields must be reduced off the spinal cord at 45.6 Gy at the midplane. Clinically positive nodes should receive a minimum dose of 81.6 Gy. To supplement the dose to clinically positive neck nodes, boosts technique may include additional electron beam ($\geq$ 9 MeV) to the posterior neck, wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 45.6 Gy at 3 cm depth.

The anterior lower neck field will be treated with 1.2 Gy per fraction at 3 centimeter depth, twice a day, with a minimum of 6 hour intervals to a total dose of 45.6 Gy in 38 fractions in 4 weeks. The total dose to the primary and clinically positive nodes will be 81.6 Gy in 68 fractions in 7 weeks. The exact time and date of each treatment should be clearly documented on the treatment record.

6.5.3 Split Course b.i.d. (Arm 3) (revised 3/15/93)

Treatment to the primary tumor and the upper neck will be given at 1.6 Gy per fraction, twice a day with a minimum of 6 hour interval, five days a week to a dose of 38.4 Gy in 24 fractions delivered in 2 1/2 weeks. This is followed by a rest period of 14 days. Subsequently, treatment will resume to deliver 1.6 Gy twice a day, with a minimum of 6 hour interval, to a reduced boost volume encompassing the

primary tumor and clinically positive nodes for an additional dose of 28.8 Gy. The total tumor dose will be 67.2 Gy in 42 fractions in 6 weeks.

Fields must be reduced off the spinal cord at 38.6 Gy at the midplane. Clinically positive nodes should receive a minimum dose of 67.2 Gy. To supplement the dose to clinically positive neck nodes, boost techniques may include additional electron beam ($\geq$ 9 MeV) to the posterior neck wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 43.2 Gy at 3 cm depth.

The anterior lower neck field will be treated only during the first segment of the therapy with 1.8 Gy per fraction at 3 cm depth, twice a day, with a minimum of 6 hour interval, to a total dose of 43.2 Gy in 24 fractions in 2 1/2 weeks. The exact time and date of each treatment should be clearly documented on the treatment record.

6.5.4 Concomitant Boost (Arm 4) (revised 3/15/93)

The large field treatment will be given at 1.8 Gy per fraction, once a day, five days a week to deliver 54 Gy in 30 fractions over 6 weeks to the primary tumor and upper neck nodes. After 32.4 Gy/18 Fx/3-1/2 weeks to the large field, start concomitant boost with 1.5 Gy/Fx/day to the boost field at least 6 hours after the large field treatment. Treat the boost field daily during the last 12 treatment days. The reduced boost volume should encompass the primary tumor and clinically positive nodes. The total tumor dose will be 72.0 Gy in 42 fractions in 6 weeks. The primary treatment fields must be reduced off the spinal cord at 45 Gy.

Clinically positive nodes should receive a minimum dose of 72 Gy. To supplement the dose to clinically positive nodes, boost techniques may include addtional electron beam ($\geq$ 9 MeV) to the posterior neck wedge pair or oblique fields. Initially clinically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm. **(4/15/95)**

The anterior lower neck field will be treated with 1.8 Gy per fraction at 3 cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks. All treatment times must be documented on the treatment record.

6.5.5 Time and Dose Modifications:

6.5.5.1 **Standard Fractionation Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks if necessary should not exceed five treatment days at a time and ten**
treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total treatment interruptions exceed ten treatment days, the case will be considered a protocol deviation.

6.5.5.2 **Hyperfractionation Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks if necessary should not exceed five treatment days at a time and ten treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total treatment interruptions exceed ten treatment days the case will be considered a protocol deviation.**

6.5.5.3 **Accelerated Hyperfractionation with Split: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks other than the planned 14 day rest period for healing of severe normal tissue reactions such as confluent radioepithelitis (mucositis). If unplanned treatment interruptions exceed 5 treatment days total, the case will be considered a protocol deviation.**

6.5.5.4 **Concomitant Boost Program: Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary should not exceed one week and should be allowed only for healing of severe mucositis. If treatment interruptions exceed five treatment days total, the case will be considered a protocol deviation.**

6.5.6 Fraction Interval: Documentation of interfraction interval must be provided on the daily treatment record.

6.5.7 Neck Dissection: If a neck dissection is planned for lymph nodes which were > 3 cm prior to RT, the dose to the involved lymph nodes may be limited to 44-50 Gy in the standard fraction arm, 50.4 in the hyperfraction arm, 38.4-43.2 Gy in the split course b.i.d. arm and 50.4 Gy in the concomitant boost arm. This information must be clearly documented in the treatment record.

6.5.8 Boost Doses:

Additional boost doses may be given through reduced fields to persistent primary tumor and or clinically positive nodes. The boost dose should not exceed 5.0 Gy for each of the fractionation schemes.

6.6 Anticipated Side Effects and Toxicities

6.6.1 Suggested maximum doses to critically sensitive normal structures:

Organ	Dose
Spinal Cord	44.0 Gy/22 fx/4 weeks (Arm 1) **(revised 8/17/92)**
	45.6 Gy/38 fx/4 weeks (Arm 2)
	38.4 Gy/24 fx/2.5 wks (Arm 3)
	45.0 Gy/25 fx/5 wks. (Arm 4)

6.6.2 Reversible radioepithelitis of oropharyngeal mucosa is expected and its timing with dose and severity should be noted and graded according to the RTOG Acute Radiation Morbidity criteria for mucous membrane (Appendix IV).

6.6.3 Also expected will be epilation of treated areas and various degrees of skin reaction in the treated area. These should be graded according to the RTOG Acute Radiation Morbidity Criteria for skin. (Appendix IV)

6.6.4 Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted, especially if supplemental feeding tube is required. See RTOG Toxicity Criteria for Acute and Late Effect grading (Appendix IV).

6.6.5 Late effects include permanent xerostomia in almost all patients and occasionally persistent dysphagia. Mandibular osteoradionecrosis will occur in 5% or less of the patients, but can be reduced by thorough dental evaluation before irradiation, which is recommended. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth where possible. At least 10 days should be allowed for healing of gingivae post-extraction.

6.6.6 Radiation-induced myelopathy can occur in less than 1% of patients providing cervical spinal cord dose remains below 40 Gy in 20 fractions in 4 weeks in Arm 1, 45.6 Gy in 38 fractions in 4 weeks in Arm 2, 38.40 Gy in 24 fractions in 2 1/2 weeks in Arm 3 or 45 Gy in 25 fx in 5 weeks in Arm 4. However, special attention should be directed in follow-up exams to any numbness, parasthesia, or L'hermitte's signs, particularly in the first 6-12 months of follow-up.

6.7 Adverse Reaction Reporting

6.7.1 Since this protocol utilizes altered fractionation radiation therapy, RTOG Headquarters and the study chairman must be notified by telephone of all fatal and life threatening toxicities (those ≥ grade 4). See RTOG Toxicity Reporting Guidelines for details. (Appendix VI).

7.0 DRUG THERAPY

Not applicable to this protocol.

8.0 SURGERY

8.1 Surgical Removal (salvage) of the primary tumor

Surgical removal (salvage) of the primary tumor should be performed only when biopsy proven persistent cancer confirms failure in the clinically abnormal site at least six weeks after completion of radiotherapy (i.e., abitrary biopsies in clinically negative sites will not constitute reason for surgical resection). The extent of resection will be dictated by the extent of tumor at the time of the initial evaluation. The primary lesion must be widely excised utilizing accepted criteria for adequate excision depending upon region involved.

Frozen section should be taken from the patient and not the surgical specimen. Marking the surgical margin in ink at the site corresponding to where the frozen section was obtained for the patient is recommended to determine if there was a sampling error in obtaining clear margins. If grossly visible palpable tumor remains unresectable at a margin that is histologically positive or when gross tumor removal is not performed, the patient will be considered to have gross residual disease. In the absence of gross residual disease, if the tumor extends within 5 mm of surgical margin the case would be considered to have close margins.

8.2 Neck Dissection

Surgical removal of the cervical lymph nodes in place of supplemented doses of irradiation may be undertaken for nodes > 3 cm prior to RT in diameter at the discretion of the surgeon/radiotherapist team. If a neck dissection is planned the dose to the involved lymph nodes may be limited to 50.0 Gy in standard fractionation arm, 50.4 Gy in hyperfractionation arm, 38.4-43.2 Gy in the split course b.i.d. arm and 50.4 Gy in the concomitant boost arm. Preservation of the accessory nerve and protection of the carotid artery will be at the discretion of the surgeon.

8.3 Closure

Primary closure with surgical defect is to be accomplished whenever possible. Reconstruction or closure with grafts, local or regional skin flaps when required is allowed at the discretion of the responsible surgeon. Close suction drainage will be routinely employed.

8.4 Operative Report

The operative report must accurately and completely describe the precise location and the extent of the primary lesion and cervical lymph node metastasis. Assessment of the completeness of the resection and results of

intra-operative frozen section should be included. Any type of closure utilized should be specified as to the primary, pedicle flap or dermal graft.

9.0 OTHER THERAPY

Not applicable to this protocol.

11.0 PATIENT ASSESSMENTS (revised 9/21/92)

11.1 Summary of the study parameter requirements is as shown:

	Prior to xrt	1 mo after xrt	1st 18 mos, every 3 mos	18 mos through year 3, every 4 mos	every 6 mos. 3-5 years
History + Physical	x	x(a)	x(a)	x(a)	x(a)
CBC	x				
Calcium	x(b)				
Serum glucose	x(b)				
Chest x-ray	x				
Biopsy of primary	x		x		
		(no earlier than 6 wks after RT & only if persistence suspected)			
CT scan or MRI of primary and neck	x	x(b)	x(b)	x(b)	

a) To include scoring of acute and late radiation effects
b) As indicated

11.2 Tumor Clearance:

Response of tumor should be documented as gauged by caliper or ruler measurements, measuring longest diameter and at right angles to it, by inspection and by palpation (use photography when applicable), should be made before therapy, weekly during therapy, and subsequently at each follow-up. Failure of clearance (persistence) will thus be documented. Time of apparent beginning regrowth will be noted. Clinically suspected persistence or recurrence should be biopsied when feasible.

11.3 Local Reaction of skin and mucous membranes should be scored (using criteria in Appendix IV) at least weekly during radiotherapy and postradiotherapy until clearance. Note concomitant use of alcohol, tobacco, or other irritants.

11.4 Survival

Record survival from start of radiation with or without local, regional or metastatic disease.

11.5 Late Effects:

At each follow-up visit, note condition of tissues (nerves, mucosa, skin, subcutaneous) and signs of soft tissue change or bony necrosis. Record any change or abnormality in CNS and/or peripheral nervous system.

11.6 Tumor assessment will be as follows: (revised 9/21/92)

Weekly during radiotherapy and the 2 week rest period.
4 weeks postradiotherapy
Every three months for first 1-1 1/2 yrs.
Every 4 months from 18 months through 3 years
Every 6 months in years 3-5 then annually thereafter until death

11.7 QOL Measurement Instruments (added 3/17/92) DISCONTINUED 12/13/00

The Quality of Life (QOL) component for this study will use three measurement instruments; two to be completed by the investigator/data manager/nurse participant and one self-report questionnaire to be completed by the patient. Each of these instruments is described below. Additional instructions for the investigator/data manager/nurse participant and patient will be included with the data forms.

11.7.1 List Performance Status Scale: (LPSS)

The LPSS is an instrument developed by List et al.[27] in collaboration with experts in the fields of otolaryngology, surgical oncology, and speech and swallowing rehabilitation science to measure performance status of the head and neck cancer patient in terms of three separate areas of functioning: (1) eating, (2) speaking, and (3) diet. Its intended use was to make effective assessments of treatment outcome, development of rehabilitation program and to gain a better understanding of the functional status of the head and neck cancer patient after a course of cancer therapy.

The LPSS consists of three separate subscales: (1) normalcy of diet, (2) understandability of speech, and (3) eating in public. The Normalcy of Diet subscale assesses the degree to which a patient is able to eat a normal diet. Ten food categories are arranged from easy-to-eat at the low end to hard-to-eat at

the high end. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed by assessing the highest ranking food the patient is able to eat. The Understandability of Speech subscale is a five-item scale which assesses the mechanism used by the patient to communicate. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. The scores are computed by assessing the degree to which the observer is able to understand the patient's speech. The Eating in Public subscale was designed to assess the degree to which the patient eats in the presence of others. There are five categories describing the patients eating patterns. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed based upon patients report of who he eats with and in what type of setting. Therefore, each patient studied will receive a total of three scores, one on each subscale. The investigator/data manager/nurse participant will determine the score on each of the subscales by performing a clinical evaluation and unstructured interview format.[27]

11.7.2 Dische Morbidity Scoring Tool (DMST)

The DMST instrument was developed by Dische[34] to measure treatment-related morbidity in head and neck cancer patients who have received a definitive course of external beam radiation therapy. Areas to be assessed include: (1) symptoms: pain, dysphagia, and taste impairment, (2) mucous membrane: erythema, ulceration, edema, thinning of the mucosa, pallor of the mucosa and telangiectasia, pigmentation-decrease, hair loss and thinning of the epidermis, and (4) temperomandibular joint and salivary gland function: trismus, dryness of the mouth, salivary consistency, time to fill in and ease of filling in. Its intended use is to objectively measure treatment related morbidity in head and neck cancer patients after receiving a course of external beam radiation therapy.

11.7.3 The Functional Assessment of Cancer Therapy for Head and Neck Questionnaire (F.A.C.T. - H&N)

This self-report questionnaire, developed by Cella et al.,[31,32] is a 47 item inventory. Of the 47 items on this questionnaire, 38 are summarized into five sub-test scores representing the following four domains of QOL to be measured; physical , social, emotional well being and relationship with their doctor. The remaining nine items are specific to the head and neck site of treatment.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 To determine whether at least one of the "experimental" treatments, (hyperfractionation (Arm 2), accelerated hyperfractionation with split course (Arm 3), or accelerated hyperfractionation with concomitant boost (Arm 4), provides improved local-regional control of advanced squamous cell carcinoma of the head and neck, as compared to the local-regional control provided by standard fractionation radiotherapy (Arm 1). The primary site and nodal disease will be scored separately.

13.1.2 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.

13.1.3 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.

13.1.4 To determine whether there exists any differences among the four treatment regimens with respect to Quality of Life **(added 3/17/92)**

13.1.2 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.

13.1.3 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.

13.1.4 To determine whether there exists any differences among the four treatment regimens with respect to Quality of Life **(added 3/17/92)**

13.2 Sample Size (4/15/95)

The external RTOG Data Monitoring Committee(DMC) reviewed this protocol at the February 1994 RTOG meeting when over 50% of the originally targeted accrual was reached. The DMC voted to continue patient accrual on all four treatment options. The DMC, however, expressed concern that the magnitude(20%) of the difference sought between each of the experimental arms and the control arm was unrealistic and felt that the study should have sufficient statistical power (.80) to detect a smaller difference, say 15%, in the two year local regional failure. During the discussion, it was pointed out that the local regional failure rate used when the study was designed was 75% at two years. The analysis of its immediate successor study, RTOG 85-27, found a two year rate of 60% for standard once-a-day fractionation radiotherapy arm. If that rate held true with the 90-03 study, there would be a loss in statistical power to detect the difference. By consensus, it was decided that the statistical section, be revised to detect a smaller difference and to account for possibly a lower failure rate for the standard arm. In the original

statistical considerations, there was no allowance made for patients who died before two years without a local regional failure. In the revised statistical section adjustment was made for them. The protocol called for twice testing for early termination of the trial. Another test was added and now there are tests to be done after 324, 648, and 1080 patients have then entered. The section on early termination has been revised to test only on local control failure rates since it was the primary endpoint for the study.

Since this study will involve the comparison of three "experimental" treatments to a single "control" treatment, the analyses will require correction for multiple comparisons using appropriate statistical procedures.[22] The sample sizes were therefore calculated using methods of sample size estimation that account for overall power and Type I error rates being affected by implementation of such multiple comparison procedures.[23] Based on the recent analysis of its immediate successor study RTOG 85-27, a two-year local-regional control rate of 0.40 is now expected for the standard fractionation patients.[26] In this study, we would like to detect with a probability *(power)* of 0.80, a difference in local-regional control rates of $\geq$15% at two years between the control group and one of the experimental treatment groups. We would also like to keep the probability of erroneously drawing a conclusion that there is a significant difference in local-regional control rates between patients on the control group and patients on any one of the experimental treatments to 5% *(Type I error rate*). In order to accomplish this we will need to accrue 223 eligible and analyzable patients to each of the four treatment groups. From the closed head and study RTOG 85-27, it was projected that 10% of patients will die without local regional failure. The sample size was initially increased by 10%. To also guard against an ineligibility rate of up to 10% the sample size was again increased by another 10% to 270 patients on each treatment arm. **Thus a total of 1080 patients will be required on the study.**

13.3 Patient Accrual (4/15/95)

As of 12/1/94, 600 patients were entered on the study. Average monthy patient accrual over the last year and over the entire study have been 15.6 and 15.8 cases respectively. Using 15.6 cases per month, it will take approximately 31 months to the complete new total accrual of 1080 cases. Thus, the patient accrual period over the entire study is estimated to be 5.75 years. If the average monthly accrual rate is less than 10 cases per month, the study will be re-evaluated for feasibility.

13.4 Randomization Scheme

Patients will be randomized to one of four treatment schedules in order to avoid any patient selection biases. The treatment allocation will be done using a randomized permuted block design within strata to balance for patient factors other than institution. Based on analyses of previous RTOG inoperable head and neck studies, three factors (site: oral cavity, oropharynx, larynx, or hypopharynx; nodal status: N0 or N+; and KPS: 90-100 or 60-80) will be used as stratifying variables.

13.5 Analyses Plans (3/17/92,4/15/95)

13.5.1 Background

With the increased sample size, another test for early termination of the trial was added. So now tests will be performed after approximately 324, 634, and 1080 patients have then entered. Early termination will be solely based on local control failure rates because it is primary endpoint for the study. The DMC's role has been clearly delineated. More details about the analyses have been added.

13.5.2 Interim Analyses to monitor the study progress:

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. The interim reports will typically contain information about the patient accrual rate with a projected completion date, data quality, compliance rate of treatment delivery with the distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. If these analyses suggest the occurrence of unexpected toxicities or unacceptable protocol compliance in one or more treatment arms, corrective action will be considered. This may result in modifications of treatment regimen(s) or possibly its termination due to toxicity. These reports will not contain any results from the treatment comparisons with respect to the efficacy endpoints. (Local regional control, disease free survival, absolute survival)

13.5.3 Significance testing for early termination

In order to ensure that patients entered on this protocol are not being randomized to an inferior treatment or being denied an obviously superior treatment, significance testing of all treatment outcomes will be conducted at the earliest point in the study that meaningful differences can be ascertained. The primary endpoint for this study is local regional failure rates at two years. This endpoint will be tested three times for early termination of the trial. First significance test was performed for the first RTOG meeting after the first 324 patients (30% of the revised total sample size of 1080) have been entered. No significant differences were reported to DMC and the trial continued as planned.

The second significance tests will be performed after 648 patients (60% of 1080 patients) have been entered into the protocol. If any experimental treatment arm shows significant inferiority to the control

arm at $p < 0.001$ in a pairwise comparison, termination of patient accrual to that treatment arm would be recommended. If all experimental arms show a highly significant advantage over the control arm at $p < 0.001$ in the pairwise comparisons, termination of the study will be recommended. The results from the tests will be then reported to the RTOG DMC for their consideration. If any of experimental treatment arm(s) is discontinued, case accrual will continue until the required sample size of 270 patients is reached for the remaining arms. At this time, there will be interim analysis of the data from the QOL and the Dische Late Morbidity tool components. The results will be presented to the DMC for their consideration of terminating further patient accrual to these components.

The third significance tests will be performed after all 1080 patients have been entered into the protocol and have been potentially followed for at least six months. If all the pairwise tests show that all the experimental arms are either superior or inferior to the control, the recommendation will be made to publish the results immediately. The results from the tests will be then reported to the RTOG DMC for their consideration. If the study is not terminated here, it will continue as planned.

13.5.4 Analysis for Reporting the Initial Treatment Results:

This major analysis will occur after each patient has been potentially followed for a minimum of 24 months unless the study is stopped earlier. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analyses with the reasons for such exclusions;
2) reporting of institutional accrual;
3) distribution of the important prognostic baseline variables by assigned treatment group;
4) observed results with respect to the primary study endpoints.

The primary hypotheses for the study are whether each of the experimental arms has different effect on two-year local regional failure rate than the control arm. All eligible patients randomized will be included in the pairwise comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. Then, a treatment difference will be considered statistically significant at a nominal alpha level of 0.047 to preserve an overall Type I error rate of 0.05 because of the three earlier tests.

The primary hypothesis of benefit with each of experiment arm will be tested using the Cox proportional hazard model with the stratification factors of primary site, N-stage, and KPS included as covariates in addition to treatment (an experimental arm vs the control arm). The benefit for an experimental arm on disease free survival, local control rate, and absolute survival will be analyzed in a similar fashion.

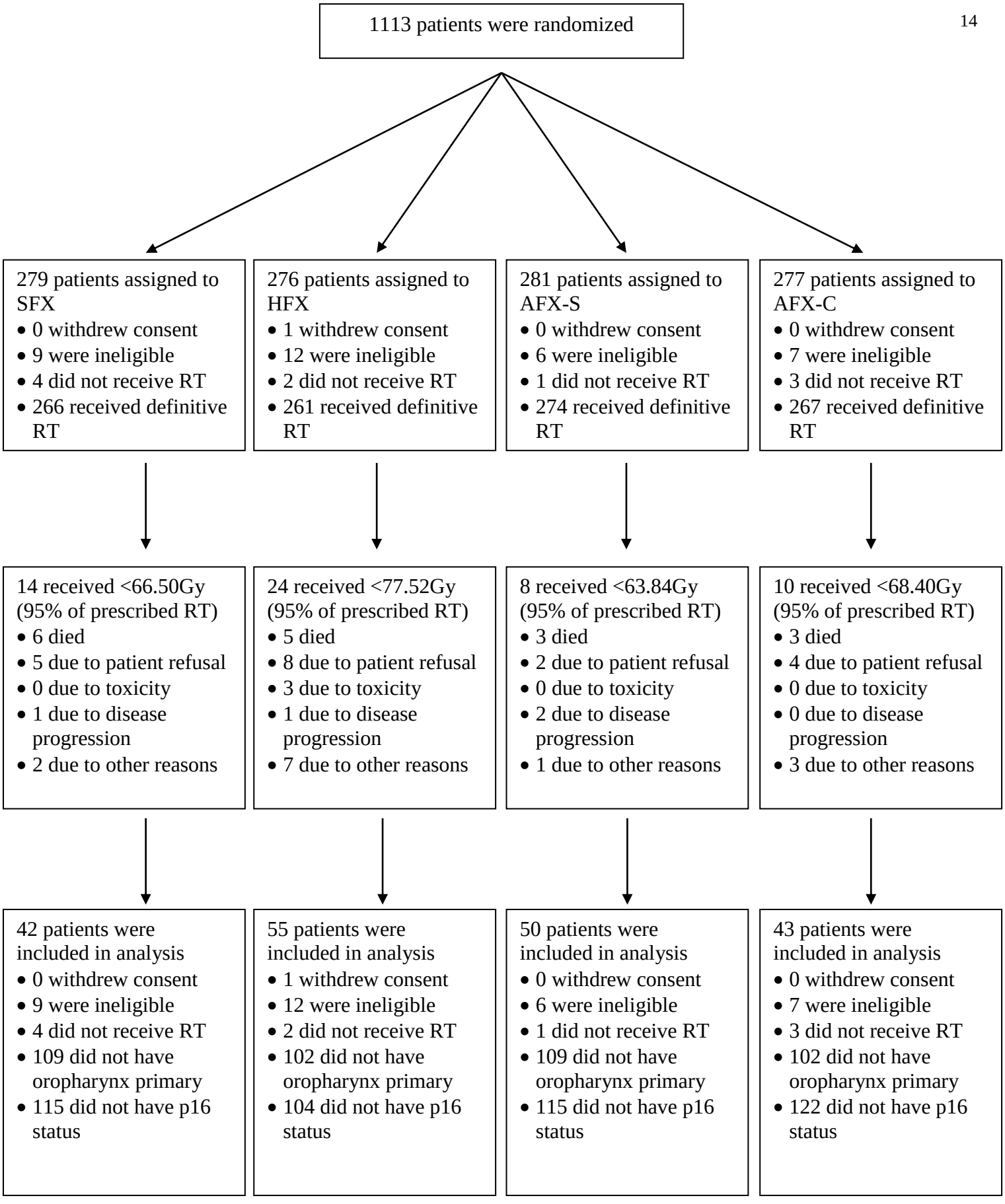
Further subgroup analyses may be conducted (depending on sample sizes of the defined subgroups) for the purpose of identifying differing patterns of treatment responses in such patient subgroup.

13.5.5 Analysis of Quality of Life

Data accrual from the Functional Assessment of Cancer Therapy (F.A.C.T. - H&N) will be analyzed using both fixed time point and quality adjusted survival methodologies. List Performance Status Scores (LPSS) will be correlated with the Karnofsky Performance Status and the two will be analyzed for sensitivity and responsiveness. The LPSS results will be compared by treatment and with subscales of the F.A.C.T. - H&N. The Dische Late Morbidity tool will be correlated with the RTOG late effects scoring system and compared for differences in the treatment arms.

14.0 ADDITIONAL THERAPY

14.1 Additional surgical treatment of the local-regional disease is allowed for head and neck if 6 weeks or more following radiotherapy, the patient manifests persistent or recurrent tumor. Systemic chemotherapy may be given at the discretion of the cancer management team for either loco-regional or distant failure. Details of any chemotherapy given must be included in the appropriate follow-up forms. Although retreatment with radiotherapy is not encouraged, irradiation may be utilized when appropriate for tumor extensions outside of the previously treated regions or for palliation of distant metastatic cancer.


1113 patients were randomized
279 patients assigned to SFX
• 0 withdrew consent
• 9 were ineligible
• 4 did not receive RT
• 266 received definitive RT
276 patients assigned to HFX
• 1 withdrew consent
• 12 were ineligible
• 2 did not receive RT
• 261 received definitive RT
281 patients assigned to AFX-S
• 0 withdrew consent
• 6 were ineligible
• 1 did not receive RT
• 274 received definitive RT
277 patients assigned to AFX-C
• 0 withdrew consent
• 7 were ineligible
• 3 did not receive RT
• 267 received definitive RT
14 received <66.50Gy (95% of prescribed RT)
• 6 died
• 5 due to patient refusal
• 0 due to toxicity
• 1 due to disease progression
• 2 due to other reasons
24 received <77.52Gy (95% of prescribed RT)
• 5 died
• 8 due to patient refusal
• 3 due to toxicity
• 1 due to disease progression
• 7 due to other reasons
8 received <63.84Gy (95% of prescribed RT)
• 3 died
• 2 due to patient refusal
• 0 due to toxicity
• 2 due to disease progression
• 1 due to other reasons
10 received <68.40Gy (95% of prescribed RT)
• 3 died
• 4 due to patient refusal
• 0 due to toxicity
• 0 due to disease progression
• 3 due to other reasons
42 patients were included in analysis
• 0 withdrew consent
• 9 were ineligible
• 4 did not receive RT
• 109 did not have oropharynx primary
• 115 did not have p16 status
55 patients were included in analysis
• 1 withdrew consent
• 12 were ineligible
• 2 did not receive RT
• 102 did not have oropharynx primary
• 104 did not have p16 status
50 patients were included in analysis
• 0 withdrew consent
• 6 were ineligible
• 1 did not receive RT
• 109 did not have oropharynx primary
• 115 did not have p16 status
43 patients were included in analysis
• 0 withdrew consent
• 7 were ineligible
• 3 did not receive RT
• 102 did not have oropharynx primary
• 122 did not have p16 status